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Case Report: Stimulation of the right amygdala induces transient changes in affective bias

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Abstract

Background—Sensitive outcome measures are needed to quantify the effects of neuromodulation in mood disorders.

Objective—This study examined the utility of a novel affective bias (AB) task in identifying transient mood changes induced by amygdala stimulation in a single rare participant.

Methods—Localized, pulsed electrical stimulation was delivered for 8 minutes during measures of AB and self-reported mood. Responses were compared with those gathered without stimulation on the same day in the same setting, using paired t-tests.

Results—Stimulation of the basolateral nucleus of the right amygdala at 50Hz, 15V, and 200μs pulse-width produced a significant positive shift in AB ($t=-2.864$, $df=53$, $p=.006$), despite equivocal findings on self-reported mood ($t=-.184$, $df=12$, $p=.857$).

Conclusion—Affective bias may be more sensitive to stimulation-induced fluctuations in mood than subjective report, suggesting utility as an outcome measure in neuromodulation studies.

Keywords

Deep Brain Stimulation; mood; depression; emotion; bioassay

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Introduction

Neuromodulation has become fertile ground for studies aimed at improving neuropsychiatric illnesses, especially mood disorders. Such studies have typically quantified efficacy in terms of self-reported mood using standard illness severity scales (1,2). A major confound to self-reported mood measures is alexithymia (a lack of insight into one's own emotional state) (3), which is frequently comorbid with chronic depression (4). In the pursuit of more sensitive and reliable outcome measures, affective bias tasks have come to the fore (5).

Affective bias (AB) is the tendency among depressed patients to interpret ambiguous or positive events as relatively negative (6). This phenomenon is especially pronounced in the rating of emotional facial expressions (7,8), a process with known amygdala involvement (9). Previous studies have shown AB in depressed patients, who interpret emotional facial expressions as either more negative or less positive than matched healthy control participants (10, 11). This experiment's first hypothesis was that measures of AB would reflect more stable aspects of mood tendency than self-report.

The current experiment used an opportunity to stimulate the brain of a chronically depressed patient who underwent intracranial monitoring prior to surgical treatment for epilepsy. Surgical epilepsy patients occasionally require depth electrodes targeted to the medial temporal lobe, including the amygdala, to definitively localize epileptogenic foci. Depth electrodes were used in the current case to stimulate the amygdala via application of electrical current at a level below threshold for eliciting epileptiform activity. The amygdala is widely implicated in mood regulation (12), but it has remained poorly characterized by stimulation studies (13–15). Based on limited previous studies (16), our second hypothesis was that such stimulation would be effective in altering mood and AB.

Methods and Materials

Participant

The patient was a 48 year-old right-handed man who underwent intracranial electrode monitoring to localize the focus of his medically intractable complex partial seizures (Appendix 1). In addition, the patient had a history of stable major depressive disorder beginning at least 1 year prior to the experiment and lasting at least 1 year after (Appendix 1). At the time of the experiment, the patient exhibited severe depression on the Beck Depression Inventory-II (BDI-II = 44) (17), and severe alexithymia on the Toronto Alexithymia Scale (TAS-20 = 77) (18). The timeline of all research-related events is presented in Appendix 2. The research protocol was approved by the Institutional Review Board of the University of Iowa, and the patient provided informed consent prior to participation.

Implantation surgery

The patient underwent surgical implantation of depth electrodes in the basolateral nuclei of the amygdala bilaterally (Supplemental Figure 1, Appendix 2). The positions of contacts spanning the basolateral nuclei were confirmed based on post-implantation MRI and they were projected on the pre-operative MRI.

Amygdala stimulation-mapping

Amygdala stimulation-mapping was used thirteen days after electrode implantation to determine the behaviorally active stimulation parameters for the AB and mood-rating tasks. Continuous stimulations of 30 seconds each were delivered to the amygdala in the following ranges: 20–130Hz, 3–20V, and 90–200 μ s pulse-width using a constant-voltage stimulator over the course of two hours on a single afternoon. The participant was unblinded to stimulation status during this protocol. During the session, EEG traces were continuously monitored. Stimulation of the left amygdala induced abnormal after-discharges on EEG with low-intensity stimulation, (likely due to proximity to the seizure focus). Therefore, the full protocol was only used on the right amygdala. Stimulation at 50 Hz, 20V, and 200 μ s pulse-width was found to elicit significant and reproducible shifts in mood (i.e., rating of sadness changed by 30%, rating of fear changed by 70%).

Affective bias and mood-rating protocols

First, to establish baselines and to allow test-retest reliabilities to be calculated for the AB and mood tasks, they were administered to the participant nine days after electrode implantation without the use of any electrical stimulation. Later, the tasks were administered a second time (thirteen days after electrode implantation) to reassess emotional state without stimulation. Then, the same day, the tasks were administered a third time under electrical stimulation to the amygdala.

In both tasks, items were presented on a computer screen and ratings were made using a visual analog scale centered at neutral with no hash marks, with negative and positive anchors on the left and right respectively. In the AB task, the patient rated the intensity and valence of facial expressions. Stimuli included three female and three male Caucasian people, whose images were modified from the MacBrain Face Stimulus Set developed by Nim Tottenham (www.macbrain.org/resources.htm). Selected faces were unambiguous exemplars of happy, sad and neutral emotion categories as evaluated with normative rating data provided by the creators. Within each identity, photographs of happy, neutral and sad facial expressions were used to generate more subtle facial expression morphs using image morphing software developed by the authors, running under Matlab (Nattick, MA). Morphs were created by interpolating pixel value and location between neutral exemplar faces (0%) and expressive exemplars (100%) using a piece-wise linear transformation over a Delaunay tessellation of manually selected control points. The task took approximately five minutes to administer.

The mood-rating task was designed to capture aspects of mood that were possible to change instantaneously as a result of stimulation (Appendix 3), based on the Symptom Checklist-90-Revised (19) and the BDI-II (17). Items were rated relative to the participant's emotional state at the moment. For example, one prompt asked, "How easy would it be to cry right now" with response anchors of "very easy" and "very difficult". The task took approximately two minutes to administer.

A constant-voltage stimulator delivered pulsed (5sec on, 5sec off), bipolar, biphasic stimulation to the right amygdala throughout the entire experiment (8 minutes). Pulsed

stimulation was used to minimize the risk of inducing epileptiform discharges, to enable monitoring of EEG throughout electrical stimulation session and to allow enough time to complete the affective bias and mood tasks. Lower-voltage stimulation (15V) was used to ensure that the patient remained blind to stimulation condition and to more clearly distinguish differential effects of stimulation on mood and AB. With stimulation on, the participant completed each task at his own pace.

Analyses

Paired samples t-tests were used to compare ratings between the stimulated and unstimulated conditions. Post-hoc tests used Pearson's correlation between the degree (percentage) of morphing pooled over happy and sad morphs and rating shift between stimulation and non-stimulation blocks. Test-retest reliability across non-stimulated blocks was evaluated with Pearson correlations of ratings between sessions for both the mood and AB tasks.

Results

AB and mood-rating paradigms were each repeated three times; first without stimulation four days prior to the stimulation experiment, then again without stimulation on the same day as the stimulation experiment, and finally with intermittent (5 sec ON; 5 sec OFF) stimulation to the right amygdala at 50Hz, 15V, and 200 μ s pulse-width.

On the AB task, the participant consistently rated the emotional facial expressions as more positive with stimulation than without (Figure 1). A paired-samples t-test indicated a significant effect of stimulation ($t=-2.864$, $df=53$, $p=.006$). A relationship was detected between the intensity of the facial expression (distance from neutral) and the participant's rating; the stronger the expression, the larger the positive shift in rating during stimulation. The correlation between intensity of the facial expression and shift in rating with stimulation was significant ($r=.44$, $p=.0007$). By comparison, a paired-samples t-test across all mood items showed a non-significant effect of stimulation ($t=-.184$, $df=12$, $p=.857$) (Figure 1).

The AB task showed high test-retest reliability ($r=.903$). By comparison, the mood-rating task showed low test-retest reliability ($r=.579$). Responses on the mood-rating task differed by as much as 38% across the four days prior to stimulation.

Discussion

The current study describes substantial changes in AB with amygdala stimulation. During stimulation, ratings of emotional facial expressions (a measure of AB) showed a statistically significant positive shift. This stands in contrast to equivocal findings from the subjective mood-rating task.

Effects of antidepressant treatments on subjective mood typically require several weeks to become clinically apparent, whether examined in the context of medications (5) or neuromodulatory treatments such as electroconvulsive therapy (ECT; 20), repeatable transcranial magnetic stimulation (rTMS; 21), and deep brain stimulation (DBS; 1). Harmer

and colleagues hypothesize that negative bias in information processing could be the element of depressive symptomatology that responds most rapidly to treatment, suggesting its utility as an outcome measure. Several studies support this hypothesis. For example, non-depressed people show a positive shift in AB (on a similar face-rating paradigm) after taking a single dose of antidepressant medication, even in the absence of subjective change in mood (22). This finding was later replicated in patients with MDD (5), where a single dose of reboxetine reversed negative AB in depressed patients, in the absence of any change in subjective ratings of mood or anxiety. Studies of AB tasks in the most common neuromodulatory treatments for mood disorders (ECT and rTMS) are wholly lacking, but some studies have recently examined the utility of other measures of affective bias in transcranial direct current stimulation (tDCS) for depression using an emotional Stroop task (23), an affective go/no-go task (24), and an emotional working memory task (25). To our knowledge, the current case is the first to describe changes in AB under intracranial electrical stimulation.

The current study is limited by the inclusion of a single rare participant who, because stimulation was carried out in separate experimental blocks, may not have been fully blind to stimulation status. Due to time constraints, we were unable to repeat the experiment with modified stimulation parameters (contact location or pulse frequency and level), and therefore cannot fully dissociate effects across stimulation parameters.

Based on the current study and the literature on the subject to date, we propose that AB tasks may provide a more sensitive and reliable outcome measure than subjective mood ratings for neuromodulation studies. The search for better outcome measures is critical because such improvements could translate to earlier and more consistent identification of treatment responders, as well as enhanced statistical power for clinical trials. This would elevate the probative value of each participant in such trials, perhaps meaning that fewer participants would be necessary or that more elaborate and elegant analyses could be used. AB tasks are also enticing for their potential use as a screening tool; several studies have shown AB tasks are able to predict treatment response (26) as well as relapse (27). In the clinical practice of DBS treatment, AB tasks could additionally be useful in the process of confirming electrode targeting, contact selection, and stimulation parameter selection. The current study offers preliminary support for the use of AB tasks for these purposes, though the current findings must be replicated in a larger sample and extended to patients receiving brain stimulation expressly for the treatment of mood disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1

Medical history

The participant was a 48-year-old right-handed male factory worker with 13 years of education. He suffered complex partial seizures emanating from the medial temporal lobe with greater than fifteen-year chronicity. MRI and FDG-PET revealed sclerosis and decreased metabolism in the left mesial temporal lobe. The patient underwent bilateral amygdala depth electrode recording as it was suspected that there might be bilateral involvement in epileptogenesis that was not measurable with surface EEG. Following a two-week period of intracranial EEG monitoring, his seizure focus was confirmed in the left anterior mesial temporal lobe which was subsequently resected. After the resection surgery, the patient has not had any seizure events.

Six months prior to the experiment, the participant endorsed items consistent with severe depression and anxiety on the Beck Depression and Anxiety Inventories (BDI-II = 35, BAI-II = 26). The participant was seen twice more for neuropsychological follow-up after the experiment, and continued to have symptoms of severe depression and anxiety (6mo: BDI-II = 36, BAI-II = 28; 12mo: BDI-II = 33, BAI-II = 38). He was generally unresponsive to multiple medications including antidepressants (fluoxetine, mirtazapine), anxiolytics (diazepam, lorazepam), and a sleep aid (zolpidem).

Appendix 2

Timeline of events

The initial measures of AB and mood occurred nine days after the implantation surgery (five days prior to the resection surgery). The second administration of non-stimulated AB and mood measures, as well as the stimulation experiment, took place thirteen days after

electrode implantation (the day before the resection surgery). The figure below describes the precise intervals between all study-related events.

Appendix 3

Amygdala depth electrode detail

The amygdala electrodes (AD-Tech Epilepsy/LTM Spencer Probe Depth Electrodes) were 1.1mm in diameter with 2.4mm platinum low-impedance contacts that delivered targeted bipolar electrical stimulation. The right amygdala electrode had four contacts with 10mm spacing. The left amygdala electrode had eight contacts with 12 mm spacing between contact 1 and 2 and 7 mm spacing between remaining contacts.

Appendix 4

Mood-rating items including overall mood, energy level, focus, ease of crying, worry, guilt, hopelessness, loneliness, positive self-regard, irritability, anxiety, suicidal ideation, and restlessness. Omitted areas of mood function (non-transient) were considered to include vegetative symptoms: sleep patterns, appetite, and interest in sex.

Specific prompts:	Anchors:
How is your mood right now?	Very depressed ----- Very happy
What is your energy level right now?	Exhausted ----- Very energetic
How focused you feel right now?	Very distracted ----- Very focused
How easy would it be cry right now?	Very easy ----- Very difficult
How worried do you feel right now?	Very worried ----- Carefree
How much guilt are you experiencing?	Strong guilt ----- No guilt
How do you feel about your future?	Quite hopeless ----- Quite hopeful
How lonely do you feel?	Very lonely ----- Not lonely at all
How much do you like yourself right now?	Not at all ----- Quite a lot
How irritable do you feel right now?	Very irritable ----- Not at all irritable
How anxious do you feel right now?	Very anxious ----- Not at all anxious
Are you having thoughts of ending your life?	Very much so ----- Not at all
How restless do you feel?	Very restless ----- Very comfortable

Figure 1.

Ratings of emotional facial expressions and mood items during stimulation minus ratings given without stimulation.

Column heights indicate difference in rating between stimulation and non-stimulation blocks of the affective bias (A) and mood-rating (B) tasks. Positive deflection indicates the item was rated as more positive during stimulation.